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Office of Surveillance and Epidemiology**

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports and drug utilization data for Emsam (selegiline transdermal system) in pediatric patients.

The selegiline transdermal system was first approved in 2006 and is indicated for major depressive disorder. The selegiline transdermal system is contraindicated in patients less than 12 years of age.

Drug utilization patterns were assessed to capture pediatric utilization of the selegiline transdermal system and to provide context for the adverse event reports submitted to the FAERS database. The outpatient retail utilization analysis showed that pediatric patients 0-17 years of age accounted for 1-2% (approximately 100 pediatric patients annually) of the total patients who were dispensed prescriptions for the selegiline transdermal system over the study period.

The Division of Pharmacovigilance (DPV) searched the FDA Adverse Event Reporting System (FAERS) Database for reports received from February 27, 2006 (FDA approval of selegiline transdermal system) to November 22, 2016. DPV reviewed all pediatric cases reported with the use of the selegiline transdermal system. There were no fatal cases, and a total of three non-fatal cases in the case series. Due to the limited number of case reports for each event, it was difficult to draw any conclusions.

The majority of serious adverse events (SAEs) reported to FDA were labeled events that are well characterized, or they were symptoms of the disorder being treated. There was one unlabeled SAEs. No new patterns or trends suggestive of new or unexpected adverse events attributable to the use of selegiline transdermal system were identified. DPV recommends no labeling changes at this time, and will continue to monitor adverse events associated with the use of the selegiline transdermal system.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Emsam (selegiline transdermal system) is available in the following strengths: 6 mg per 24 hours, 9 mg per 24 hours and 12 mg per 24 hours. It is a monoamine oxidase inhibitor indicated for the treatment of major depressive disorder. The selegiline transdermal system should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm once every 24 hours.

- Initial Treatment: The recommended starting dose and target dose for EMSAM is 6mg per 24 hours. Based on clinical judgment, dose increases should occur in increments of 3mg per 24 hours (up to a maximum dose of 12mg per 24 hours) at intervals of no less than 2 weeks.
- Dietary Modifications with EMSAM 9mg per 24 hours and 12mg per 24 hours: Tyramine-rich foods and beverages should be avoided beginning on the first day of EMSAM 9mg per 24 hours or 12mg per 24 hours treatment, and should continue to be avoided for 2 weeks after a dose reduction to EMSAM 6mg per 24 hours or following the discontinuation of EMSAM 9mg per 24 hours or 12mg per 24 hours.¹

This review was initiated by the following PREA pediatric labeling change on September 10, 2014:

Multi-center, randomized, double-blind, placebo-controlled, flexible-dose trial in 308 adolescents 12 – 17 years failed to demonstrate efficacy. The selegiline transdermal system should not be used in patients less than 18 years. Use in patients less than 12 years is contraindicated because of the potential for a hypertensive crisis, which may be increased compared to adolescents and adults based on limited PK data suggesting higher exposure even at the lowest dose. Adverse events were similar to those observed in adults postmarketing study.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

EMSAM (selegiline transdermal system)

-----CONTRAINDICATIONS-----

- Serotonergic drugs: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), clomipramine and imipramine, meperidine, tramadol, methadone, pentazocine, and propoxyphene; and the antitussive agent dextromethorphan should not be used with EMSAM because of a risk of serotonin syndrome (4, 5.2).

- Carbamazepine should not be used with EMSAM (4, 5.3).
- After stopping treatment with contraindicated medication, a time period equal to 4 to 5 half-lives (approximately one week) of the drug or any active metabolite should elapse before starting therapy with EMSAM. Because of the long half-life of fluoxetine and its active metabolite, at least 5 weeks should elapse between discontinuation of fluoxetine and initiation of treatment with EMSAM (4).
- At least 2 weeks should elapse after stopping EMSAM before starting therapy with a drug that is contraindicated with EMSAM (4).
- EMSAM is contraindicated in patients less than 12 years of age (4, 8.4).
- Pheochromocytoma (4).

-----WARNINGS AND PRECAUTIONS-----

- Tyramine-Induced Hypertensive Crisis: Patients receiving EMSAM 9 mg per 24 hours and 12 mg per 24 hours should follow the recommended dietary modifications (5.3).
- Blood Pressure Elevation Related to Concomitant Medication: monitor blood pressure if EMSAM is used with any of the following drugs: buspirone, amphetamines, or cold products or weight-reducing preparations that contain sympathomimetic amines (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine) (5.3).
- Activation of Mania/Hypomania: Use cautiously in patients with a history of mania (5.4).
- External Heat: Avoid exposing the EMSAM application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight (5.5).

-----ADVERSE REACTIONS-----

Adverse Reactions occurring at an incidence of 2% or More Among EMSAM-Treated Patients and greater than placebo: Application site reaction, headache, insomnia, diarrhea, dry mouth, dyspepsia, rash, pharyngitis, sinusitis (6.2).

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Nursing Mothers: Discontinue nursing or discontinue the drug (8.3).
- EMSAM is contraindicated in patients under age 12 years and is not recommended in patients 12 to 17 years of age (4, 8.4)

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary drug utilization databases were used to conduct these analyses. Detailed descriptions and limitation of the databases are included in Appendix A.

2.1.1 Data Sources Used

Sales Distribution Data

The IMS Health, IMS National Sales Perspectives™ database was used to obtain the nationally estimated number of units sold for the selegiline transdermal system from manufacturers to all U.S. channels of distribution. The sales distribution data represent the amount of product sold from manufacturers to pharmacies and other setting of care; it does not reflect what is being sold to or administered to patients directly.

Outpatient Retail Settings

The IMS Health Total Patient Tracker (TPT) database was used to provide the nationally estimated number of patients stratified by patient age (0-17, and 18 years and older) who received dispensed prescriptions for Emsam (selegiline transdermal system) from U.S. outpatient retail pharmacy settings from December 2011 through November 2016, annually.

2.2 RESULTS

2.2.1 Sales Distribution Data

2.2.1.1 Settings of Care

Sales data for the selegiline transdermal system by the number of packages sold from manufacturers to all U.S. settings of distribution indicated that approximately 75% of sales were to outpatient retail pharmacies, 10% to non-retail settings and 15% to mail order/specialty pharmacies in 2016.¹ Accordingly, only U.S. outpatient retail pharmacy utilization patterns were examined for the selegiline transdermal system in this drug utilization review. Data from mail-order/specialty pharmacies and non-retail settings, such as clinics and hospitals, were not included in this review.

2.2.1.2 Patient Data

Table 1 shows the nationally estimated number of patients who received a prescription for the selegiline transdermal system from U.S. outpatient retail pharmacies stratified by age (0-17 and

¹ IMS Health, IMS National Sales Perspectives™ Database. June 2014-November 2016. Extracted January 2017. File: NSP 2016-2433 aripiprazole 01-23-17.

18+) for 12-month periods from December 2011 through November 2016. Pediatric patients aged 0-17 accounted for 1-2% of total patients (approximately 100 pediatric patients annually) who received a dispensed prescription for the selegiline transdermal system during each 12-month period examined.

Table 1 Nationally estimated number of patients dispensed a prescription for the selegiline transdermal system from U.S. outpatient retail pharmacies, from December 2011 through November 2016, annually.

Age	Dec2011 - Nov2012		Dec2012 - Nov2013		Dec2013 - Nov2014		Dec2014 - Nov2015		Dec2015 - Nov2016	
	Patients (N)	Share(%)	Patients (N)	Share(%)	Patients (N)	Share(%)	Patients (N)	Share(%)	Patients (N)	Share(%)
Grand Total	7,744	100	7,954	100	7,279	100	6,499	100	6,087	100
0 - 17	125	1.6	100	1.3	92	1.3	71	1.1	86	1.4
18+	7,632	98.6	7,867	98.9	7,190	98.8	6,384	98.2	5,949	97.7
Unknown Age			3	0.0	43	0.6	75	1.2	72	1.2

*Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study.

** Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-17 years include patients <18 years of age (17 years and 11 months).

***Patient age subtotals may not sum exactly due to patients aging during the study, and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

Source file: IMS Health, Total Patient Tracker™. Years 2011-2016. Extracted April 2017. File: TPT 2016-2628 Emsam Peds 4-16-2017.xlsx

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	November 22, 2016
Time Period of Search	February 27, 2006* - November 22, 2016
Search Type	Quick Query
Product Name(s)	Emsam
NDA(s)	021336; 021708
Search Parameters	All ages, all outcomes, worldwide

Table 3.1.1 FAERS Search Strategy

* US Approval date

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total Adult and pediatric FAERS reports*February 27, 2006 – November 22, 2016 with the selegiline transdermal system

	All reports (US)	Serious [†] (US)	Death (US)
Adults (≥ 18 years)	1025 (1021)	200 (197)	10 [‡] (10)
Pediatrics (0 - <18 years)	4 (4)	2 (2)	0 (0)

* May include duplicates and transplacental exposures, and have not been assessed for causality

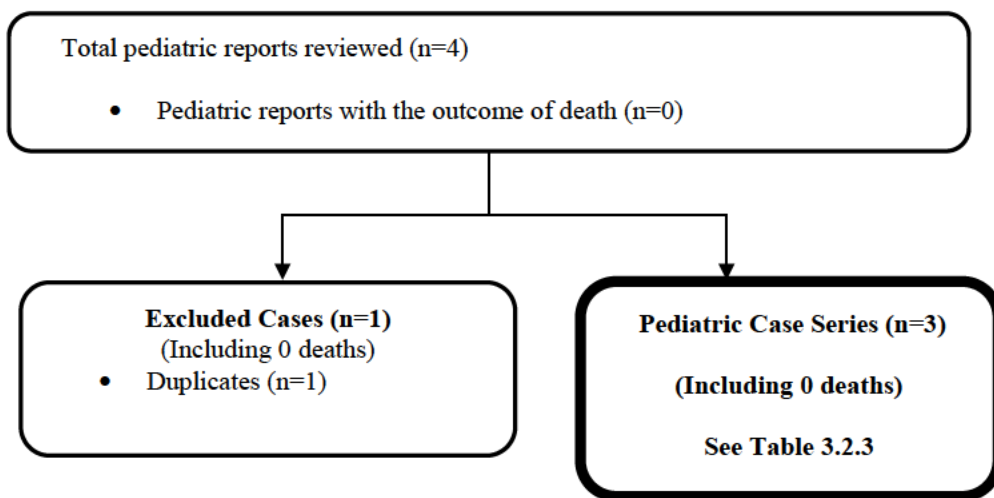
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡ Does not include null age death reports

3.2.2 Pediatric Cases in FAERS

We identified four pediatric reports (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4**.

Figure 3.2.2 Selection of Serious Pediatric Cases with the selegiline transdermal system



3.2.3 Characteristics of Pediatric Case Series

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.3 Characteristics of Pediatric Case Series with the selegiline transdermal system (N=3)

Age (n=3)	12- < 18 years	3
Sex	Male	1
	Female	2
Country	United States	3
Reported Reason for Use	Depression	2
	Unknown	1
Serious Outcome (N=1)*	Hospitalized	1

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no pediatric deaths in the case series.

3.4 SUMMARY OF NON-FATAL PEDIATRIC ADVERSE EVENT CASES (N=3)

Unlabeled Events: Psychotic Disorder, Screaming

A 13 year-old female experienced uncontrolled screaming and a psychotic break while participating in a Phase IV, Double-Blind, Placebo-Controlled, Randomized, Flexible Dose Study of the Safety and Efficacy of the selegiline transdermal system in Adolescents With Major Depression. She reported no concomitant medications or medical history prior to entering the study. Three days after beginning therapy with the selegiline transdermal system, the subject reportedly locked herself in her apartment bathroom and began screaming. She had woken up from a bad dream and “expressed having intrusive thoughts.” She was removed from the bathroom by apartment security and taken to the office. The police were called and the patient was taken to the hospital and admitted. The patient had no current medical problems and no history of sexual abuse or drug abuse. She did have a history of family conflicts for which she received therapy. The subject remained “unpredictable.” She “expressed a desire to push her sister into the train tracks, had imaginary friends, and an inappropriate smile (she said her thoughts made her smile).” The treating facility described the event as a psychotic break, but further details were not available. The treatment was unblinded and the subject had been randomly assigned to selegiline transdermal system 6 mg/day. The selegiline transdermal system was discontinued, but the patient “continued having ‘thoughts’, poor participation, and bizarre behavior following the discontinuation.” The patient was discharged on no medications and at the time of discharge she was “alert with normal speech, average fund of knowledge, oriented x 4, memory impaired, fair attention and concentration, unrealistic judgement, concrete thought process, poor insight, restricted affect, appropriate mood, normal motor activity.”

Labeled Event: Insomnia

Insomnia is labeled in the Warnings & Precautions and Adverse Reactions sections. The occurrence of insomnia is consistent with the known risk in the labeling and no increased severity was observed in the report. Below is a summary of the case. This was a non-serious adverse event.

Insomnia (n=1)

A 16 year-old male patient experienced trouble falling asleep while receiving selegiline transdermal system 9 mg/day for the treatment of depression. The patient's mother reported she believed it is related to the use of the selegiline transdermal system. The patient reportedly did not have any other changes to medications, medical history, lifestyle, or an increase in stressors at the time of the event. The selegiline transdermal system was continued and the event was reported as ongoing.

Labeled Events: Dizziness, Hyperhidrosis, Hypotension

Dizziness is labeled in the Warnings & Precautions, Adverse Reactions, and Overdose sections. Sweating is labeled in the Warnings & Precautions section. Hypotension is labeled in the Overdose section. The occurrence of dizziness, hyperhidrosis, and hypotension is consistent

with the known risk in the labeling and no increased severity was observed in the report. Below is a summary of the case.

Dizziness, Hyperhydrosis, Hypotension (n=1)

A 16-year-old female reported that she developed dizziness while receiving selegiline transdermal system 9 mg. The dose of the selegiline transdermal system was decreased to 6mg and the patient's mother reported that her daughter "got up in the morning feeling lightheaded/dizzy, sweaty/clammy and has low blood pressure." No additional details were provided.

4 DISCUSSION

Of the three reports reviewed in pediatric patients, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths directly associated with the selegiline transdermal system in this case series. Due to the limited number of case reports for each event, it was difficult to draw any conclusions.

The overall number of patients who received an outpatient dispensed prescription for the selegiline transdermal system from U.S. outpatient retail pharmacies declined over the time period examined, and pediatric patients 0-17 years old accounted for approximately 1-2 % of the total patients. However, pediatric utilization cannot be validated due to the lack of access to patient medical records. It is important to note that this may be due to issues in documentation, such as documenting the date of prescription rather than the date of birth. Furthermore, our analyses only focused on the outpatient retail setting and might not apply to other settings of care such as inpatient setting and clinics where the selegiline transdermal system may be used.

5 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with this drug at this time.

6 RECOMMENDATIONS

Continue standard pharmacovigilance monitoring.

7 REFERENCES

1. Emsam [package insert]. Morgantown, WV: Somerset Pharmaceuticals; March 2015.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that the selegiline transdermal system was distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives™ database. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

IMS Health, Total Patient Tracker (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

Please note that subtotals may not sum exactly due to rounding. Because of patients aging during the study period, patients may be counted more than once in the individual age categories. For this reason, summing across years is not advisable and will result in overestimates of patient counts.

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-

marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH THE SELEGILINE TRANSDERMAL SYSTEM (N=4)

FAERS Case #	Version #	Manufacturer Control #
7064701	2	US-MYLANLABS-2009S1012699
7072989	1	(blank)
10043939	2	US-MYLANLABS-2013S1008316
6491032	1	US-BRISTOL-MYERS SQUIBB COMPANY-13918800

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/s/

COURTNEY M SUGGS
05/22/2017

SHEKHAR H MEHTA
05/23/2017

RAJDEEP K GILL
05/24/2017
Drug use data has been cleared by data vendors.

VICKY C CHAN
05/24/2017

GRACE CHAI
05/30/2017

CINDY M KORTEPETER
05/30/2017